A Cohort Study of Stomach Cancer in a High-Risk American Population

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Demographic, smoking and dietary information was obtained from a cohort of 17,633 white American men, largely of Scandinavian and German descent, who responded to a mailed questionnaire in 1966. After 20 years of follow-up, 50% to 90% increases in mortality from stomach cancer (75 deaths) were found among foreign-born, their children, and among residents of the North Central states. An association was seen with low educational attainment and laboring or semiskilled occupations, primarily among immigrants and their children. Risk was elevated in subjects who regularly smoked cigarettes (RR = 2.6, 95% CI = 1.1 to 5.8). A significant dose–response trend was observed, with subjects who smoked 30 or more cigarettes per day having more than a five-fold increased risk compared with those who never smoked. Elevated risks were also found for pipe smoking and smokeless tobacco use, but not for alcohol consumption. Analysis of dietary consumption of nine food groups revealed no significant associations with stomach cancer. However, total carbohydrate intake and a few individual food items (salted fish, bacon, cooked cereal, milk, and apples) were associated with increased risk. The findings of this prospective study of a high-risk population add to the limited evidence relating tobacco consumption to stomach cancer risk and suggest clues to ethnic, geographic, and dietary risk factors. *Cancer* 68:672–678, 1991.

ALTHOUGH STOMACH CANCER MORTALITY and incidence rates have declined significantly in the United States and other industrialized countries, stomach cancer is still the leading cause of cancer mortality in many countries.[1–4] The downward trends in certain countries, along with substantial geographic variation in rates and decreased risk among migrants from high-risk to low areas, suggest that environmental factors are of pri importance.[1,5] However, the responsible agents hav been clearly identified, although salt-preserved food other dietary items are suspected, whereas fresh fruit vegetables are thought to be protective.[1] Here we r on stomach cancer among over 17,000 male insur policy holders classified by smoking history and diet w mortality experience has been followed for 20 years. T subjects, many of whom were of Norwegian, Swedis German descent and resided in the North Central s formed a cohort at high risk of stomach cancer.[5–8]

Methods

This study was an outgrowth of prior investiga into risk factors for gastrointestinal cancers among dents of Norway and Norwegian-born immigrants t United States.[9] In October 1966, a questionnaire was to 26,030 white male life insurance policy holders,

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15 and older, of the Lutheran Brotherhood Insurance Company, whose headquarters is in Minneapolis, Minnesota.[10] To increase the number of men of Norwegian descent, recipients were limited to residents of California, New Jersey, and Washington and the North Central states of Michigan, Minnesota, Missouri, North Dakota, Ohio, and Wisconsin. Because the recipients also included many persons of Swedish or German descent and because stomach cancer mortality was reported to be similarly elevated among immigrants from Norway, Sweden, and Germany,[5] the focus of the analysis became risk factors among a population of largely Norwegian, Swedish, or German descent. Over 47% of the study subjects either were foreign-born or had at least one foreign-born parent (*i.e.*, second-generation Americans), and of these, over 76% were born in either Norway, Sweden, or Germany or had at least one parent born in one of these countries.

The questionnaire covered demographic variables, tobacco, and alcohol use, dietary and other factors, as of 1966. By March 1967, the enrollment closing date, three mailings yielded 17,818 returned questionnaires for a response rate of 68.5%. Compared with the overall US population in the mid-1960s, a much larger proportion of the respondents were farmers (31% *versus* 4.5%), whereas a smaller proportion were laborers or in semiskilled occupations (11% *versus* 27%),[11] and a slightly larger proportion never smoked cigarettes (30% *versus* 25%).[12]

The dietary section of the questionnaire included 35 foods that were grouped into nine categories: meats, poultry, fish, eggs, dairy products, breads, fruits, vegetables, and cruciferous vegetables. Data from 185 respondents were excluded because more than ten food items were unanswered. Seventy-one percent of the 17,633 subjects included in the final analysis had no missing data on any food item, 25% had fewer than five missing food items, and 4% had between five and ten missing food items. For the analyses of food groups and nutrients, we imputed intake for the missing food items, using the median intake value for the remaining subjects, stratified by urban/rural, educational attainment and age categories. Consumption of various nutrients was calculated using information on average portion size and nutrient composition derived from the Second National Health and Nutrition Examination Survey (NHANES II)[13] and from US Department of Agriculture food composition tables.[14] However, the 1966 questionnaire was not designed to capture all sources of major nutrients in the US diet.

Death certificates for the cohort were coded for underlying cause of death, other contributory causes of death, and other significant conditions by a nosologist at the Minnesota State Department of Health. In 1986, after 20 years and over 287,000 person-years of follow-up, 4513 deaths had occurred among active policy holders (26% of the cohort), 9093 active policy holders were known to be alive (52% of the cohort), and 4027 respondents (23% of the cohort) were lost to follow-up due to maturation or lapse of their policies. At 11.5 years of follow-up in 1978, comparisons of study respondents with nonrespondents and with respondents who had been lost to follow-up showed no significant differences with respect to age, urban/rural residence, vital status, or cause of death.[10]

A generalized Poisson regression program for modelling hazard functions with grouped data was used to calculate age-adjusted relative risks (RR) and 95% confidence intervals (CI).[15,16] Data were stratified by year of birth (5-year intervals) and, in the case of demographic and dietary variables, also by current cigarette use. Relative risks were calculated for each variable, summarized over all strata. For variables found to be associated with stomach cancer, mortality was analyzed separately according to immigrant status and age. For certain foods, analyses were performed to determine whether a risk differential existed between mortality close to the time of interview and many years afterward. Dose response was tested by calculating a chi-square estimate for linear trend in the means of each category.[16]

Results

In 1986, after 20 years of follow-up, there were 1033 cancer deaths, including 75 from stomach cancer. Stomach cancer was listed as the main or underlying cause of death in 72 subjects, and in three as a contributory cause.

As shown in Table 1, risk of stomach cancer was increased among the foreign-born and first-generation

TABLE 1. Relative Risks* for Stomach Cancer Mortality by Immigrant Background

Respondent's nativity†	RR	95% CI	No. of deaths	No. of subjects	Median age at interview (yr)
Native born of native parents	1.0	—	23	9037	46
Native born of foreign parent(s)‡	1.5	0.90–2.54	44	7407	55
Foreign born§	1.7	0.75–4.01	8	924	62

RR: relative risks; CI: confidence interval.
* Adjusted for yr of birth (5-yr intervals) and current cigarette smoking.
† Unknowns excluded.
‡ Includes 26 deaths among 4905 subjects of Norwegian or Swedish parentage (RR = 1.3, CI = 0.74–2.36 and eight deaths among 1040 subjects of German parentage (RR = 1.9, CI = 0.83–4.26).
§ Includes five deaths among 450 subjects born in Norway or Sweden (RR = 2.1, CI = 0.76–5.72).

Americans. The foreign-born subjects tended to be older (their median age at interview was 62 *versus* 55 for first-generation Americans and 46 for American-born subjects of American-born parents), but excess risk persisted after adjusting for these age differences. Fifty percent of the foreign-born subjects were born in Norway or Sweden. Sixty-six percent of the first-generation Americans had a Norwegian or Swedish parent, whereas another 14% had a German-born parent. Consistent variations according to country of origin were not observed for the foreign-born and first-generation Americans. Residents of the North Central states (83% of the subjects) were at higher risk than residents of California, New Jersey, or Washington (68 *versus* seven cases, RR = 1.9, CI = 0.87 to 4.14). This difference persisted after stratifying by immigrant status, as well as immigrant status together with either education or occupation.

Level of education was inversely related to stomach cancer risk (Table 2). Compared with subjects who attended college, subjects who did not go beyond junior high school had a relative risk of 1.8 (CI = 0.98 to 3.38). Subjects who did not go beyond high school had an intermediate relative risk. However, this educational gradient was apparent only for foreign-born and first-generation Americans. Among the foreign-born and first-generation Americans, the RR associated with no more than a junior high school education was 2.3 (CI = 1.02 to 5.03), whereas among subjects with American-born parents, it was 1.0 (CI = 0.31 to 3.17). Laboring and semiskilled occupations, but not farming, had elevated risks compared with professional, technical, and managerial occupations. These increased risks also were most apparent for foreign-born and first-generation Americans, although the numbers of cases in some of the occupational categories were small. There was no association with urban/rural residence, number of years lived on a farm, or birth on a farm.

TABLE 2. Relative Risks* for Stomach Cancer Mortality by Socioeconomic Variables†

	RR	95% CI	No. of deaths	No. of patients
Highest level of schooling				
College	1.0	—	15	6019
High school	1.5	0.80–2.86	26	6898
Elementary or junior high school	1.8	0.98–3.38	34	4644
Occupation				
Professional, technical, manager	1.0	—	16	4796
Clerical skills, sales	1.5	0.66–3.41	9	1854
Craftsman	1.2	0.59–2.55	13	2933
Semiskilled	1.8	0.83–3.89	11	1643
Laborer	1.8	0.41–7.74	2	300
Farm manager, farm laborer	1.0	0.54–1.99	21	5469

RR: relative risks; CI: confidence interval.
* Adjusted for year of birth (5-year intervals) and current cigarette smoking.
† Unknowns excluded.

TABLE 3. Relative Risks* for Stomach Cancer Mortality by Cigarette Use†

	RR	95% CI	No. of deaths	No. of patients
Cigarette use				
Never any tobacco	1.0	—	8	3507
Tobacco use but never cigarettes	1.5	0.52–4.38	6	1420
Ever any cigarette use	2.1	0.98–4.38	49	11666
Present/past occasional use only	0.7	0.20–2.77	3	1750
Past regular use (exsmokers)	2.2	0.99–4.91	24	4797
Current regular use‡	2.6	1.14–5.81	22	5113
1–19/d	2.2	0.84–5.97	8	1817
20–29/d	2.0	0.73–5.63	7	2243
30+/d	5.8	2.07–16.19	7	973
Pack-years‡				
<0.01	1.0	—	17	5332
0.01–17.99	1.3	0.61–2.70	12	3749
18.00–32.99	1.4	0.67–3.10	11	3446
33+	2.3	1.23–4.33	24	3456

RR: relative risks; CI: confidence interval.
* Adjusted for yr of birth (5-yr intervals).
† Unknowns excluded.
‡ P for trend < 0.01.

As shown in Table 3, subjects who were current cigarette smokers in 1966 had a significantly increased risk of stomach cancer compared with those who never used any tobacco (RR = 2.6; CI = 1.14 to 5.81). Risk among exsmokers was almost as high (RR = 2.2; CI = 0.99 to 4.91). Furthermore, there were significant increases in risk with increasing daily cigarette consumption and pack-years of smoking, with the highest risk among smokers of 30 or more cigarettes per day (RR = 5.8; CI = 2.07 to 16.19). Stratification by educational level, immigrant status, occupation, or residential region did not alter these results. There was no significant effect of age at which smoking began, but the association with smoking appeared stronger for younger cases. The age-adjusted RR for stomach cancer mortality at age 67 or less was 4.8 (CI = 1.10 to 21.37) among all current smokers and 9.4 (CI = 1.83 to 48.74) among those who smoked 30 or more cigarettes per day, whereas the age-adjusted RR after age 67 was 1.6 (CI = 0.54 to 4.56) among all current smokers and 3.8 (CI = 0.75 to 18.91) among those who smoked 30 or more cigarettes per day.

Regular pipe smokers had an elevated risk compared with subjects who never used any tobacco (13 cases among 1356 users; RR = 4.4; CI = 1.84 to 10.72). Although most pipe smokers were either current or former cigarette smokers, stratification by pack-years of cigarette smoking still yielded an elevated risk (RR = 2.9; CI = 0.97 to 8.81). No significant excess risk was associated with cigar smoking (RR = 1.3; CI = 0.30 to 5.59). An increased risk

TABLE 4. Relative Risks* for Stomach Cancer Mortality by Levels of Consumption of Various Food Groups†

	Lowest quartile		Second quartile			Third quartile			Fourth quartile			
Food group	RR	Deaths	RR	CI	Deaths	RR	CI	Deaths	RR	CI	Deaths	Trend
Meats	1.0	19	1.1	0.59–2.10	19	1.4	0.77–2.65	22	0.9	0.46–1.80	15	NS
Fish	1.0	8	2.0	0.90–4.45	24	2.7	1.23–5.89	29	1.5	0.63–3.61	14	NS
Dairy	1.0	21	1.2	0.67–2.26	21	1.1	0.61–2.10	20	1.2	0.61–2.44	13	NS
Breads	1.0	16	0.9	0.45–1.83	16	0.8	0.38–1.61	14	1.6	0.87–2.96	29	NS
Fruits	1.0	14	1.3	0.63–2.56	18	1.5	0.79–3.02	22	1.5	0.75–2.93	21	NS
Vegetables	1.0	20	1.1	0.61–2.11	20	1.1	0.59–2.09	19	0.9	0.48–1.78	16	NS
Cruciferous vegetables	1.0	14	1.6	0.78–3.05	21	1.4	0.73–2.82	21	1.3	0.67–2.68	19	NS

RR: relative risks; CI: confidence interval; NS: not significant.
* Adjusted for yr of birth (5-yr intervals) and current cigarette smoking.
† Poultry and eggs are excluded because each of these groups consisted of just one food item.

of stomach cancer was seen among current or former users of smokeless tobacco (chewing tobacco or snuff) compared with tobacco abstainers (18 cases; RR = 2.3; CI = 0.98 to 5.22). Stratification by pack-years of smoking reduced this risk estimate (RR = 1.6; CI = 0.58 to 4.50), but a significant excess risk was found among nonsmokers who used smokeless tobacco (three cases; RR = 3.8, CI = 1.00 to 14.32).

Alcohol use, as measured by consumption of beer and hard liquor (*e.g.*, whiskey, gin, cognac), showed no relationship with stomach cancer risk. The RR for the highest levels of beer and hard liquor consumption (14 or more drinks per month) were both 1.1, as was the RR for the highest quartile of combined beer and hard liquor consumption.

Table 4 shows the risks associated with intake of various food groups. No group showed a significant positive or negative trend, although risks were elevated for the intermediate levels of fish consumption.

As shown in Table 5, after controlling for age and smoking status, several of the 35 individual food items were associated with increased stomach cancer risk. Subjects who ate salted fish at least once per month had twice the risk of those who consumed it less frequently. This increased risk was most apparent among residents of the North Central states (RR = 2.1, CI = 1.08 to 4.13) and immigrants and first-generation Americans (RR = 2.2, CI = 0.97 to 4.77). Immigrants and first-generation Americans with less than a high school education who ate salted fish at least once a month had an RR of 5.7 (CI = 1.19 to 27.58) compared with college-educated immigrants and first-generation Americans who never ate it.

Moderate but not high intake of fresh or frozen fish was also associated with increased risk (Table 5). Bacon consumption was associated with elevated risk, but again the trend was not smooth. Subjects in the highest consumption categories of milk and apples (eaten in season) had significantly higher risks than subjects with the lowest intake of these items, but only cooked cereal and apples showed significantly increasing trends. Of the nutrient indices examined, only carbohydrates showed a significant trend, although the food items in the questionnaire captured only about 70% of total carbohydrate consumption in a typical American diet.[17]

Discussion

This prospective study of gastric cancer mortality among a cohort of initially healthy men of predominantly Scandinavian and German origin revealed associations consistent with the elevated rates reported among immigrants from high-risk regions including Scandinavia and Germany.[5] Stomach cancer mortality has long been known to be elevated in the North Central region of the United States, due at least partly to high concentrations of immigrants from Northern Europe.[6–8] Our findings suggest that the excess risk in this area is not entirely due to foreign birth or having an immigrant parent, even after accounting for socioeconomic differences between subjects in the North Central states and those in other regions. We found, however, that elevated risks associated with low educational attainment and semiskilled or laboring occupations were primarily among foreign-born and first-generation Americans, pointing to underlying risk factors common to low socioeconomic status and immigrant background. Previous findings suggesting that farmers are at excess risk[18] were not confirmed by our study.

A principal finding of this study was the excess risk and dose–response gradient associated with cigarette smoking. Several case–control studies[19,20] have reported significant associations between cigarette smoking and stomach cancer, with 1.3-fold to three-fold increased risks among smokers. However, only a few of these studies have shown a dose–response relationship,[21–23] whereas others have found no association at all.[17,24,25] At least nine prospective studies have examined the relationship between stomach

TABLE 5. Relative Risks* Stomach Cancer Mortality by Levels of Consumption of Selected Foods and Nutrients†

	RR	95% CI	No. of deaths	No. of patients	Trend‡
Salted fish (times/mo)					NS
Never	1.0	—	27	7842	
<1	1.0	0.58–1.83	21	5339	
≥1	1.9	0.98–3.59	14	1820	
Used before but not currently	1.3	0.61–2.62	10	1805	
Fresh or frozen fish (times/mo)					NS
<1	1.0	—	21	6956	
1–2	2.1	1.21–3.55	37	5835	
≥3	1.1	0.55–2.08	15	4178	
Used before but not currently	1.0	0.13–7.39	1	270	
Bacon or side pork (times/mo)					NS
<3	1.0	—	14	4910	
3–5	1.7	0.88–3.27	25	5221	
6–13	2.0	1.02–3.90	22	3867	
≥14	1.4	0.63–3.06	11	2753	
Used before but not currently	1.0	0.13–3.05	1	730	
Milk (glasses/d)					NS
<1	1.0	—	17	4328	
1	1.4	0.76–2.74	21	3795	
2–3	0.9	0.45–1.70	18	5986	
≥4	2.4	1.10–5.04	11	1655	
Used before but not currently	1.2	0.50–2.68	8	1739	
Cooked cereal (times/mo)					$P < 0.05$
Never	1.0	—	5	1583	
<3	0.8	0.30–2.25	16	5258	
3–5	1.0	0.36–2.79	14	3488	
6–13	1.3	0.46–3.48	15	2766	
14–29	1.7	0.60–4.78	13	1646	
≥30	1.8	0.56–5.66	7	878	
Used before but not currently	0.5	0.11–1.95	3	1808	
Apples in season (times/mo)					$P < 0.05$
<1	1.0	—	4	1795	
1–2	1.4	0.41–4.85	7	2266	
3–5	2.4	0.80–6.95	19	3762	
6–13	2.1	0.70–6.08	19	4661	
≥14	3.2	1.10–9.17	25	4269	
Used before but not currently	0.6	0.07–5.42	1	631	
Carbohydrates (kg/mo)					$P < 0.05$
0.00–4.01	1.0	—	15	4408	
4.01–5.04	0.9	0.41–1.79	13	4408	
5.04–6.25	1.7	0.87–3.18	24	4409	
6.25–14.7	1.6	0.85–3.15	23	4408	

RR: relative risks; CI: confidence interval; NS: not significant.
* Adjusted for yr of birth and current cigarette smoking.
† Unknowns excluded.
‡ Excludes "used before but not currently."

cancer and smoking.[19,26,27] Whereas most reported small increases in risk (up to 1.8-fold) for current male smokers, only two showed a significant dose–response effect.[19,27]

The stronger relation of smoking to mortality at younger ages may be due to chance. However, any effects of smoking may be more conspicuous in recent cohorts that have a lower overall risk of stomach cancer. Also, 1976 to 1987 data from the National Cancer Institute's Surveillance, Epidemiology and End Results Program indicate that among white males, age-specific incidence rates for adenocarcinoma of the gastric cardia are the same as for adenocarcinoma of more distal stomach sites through age 64, after which rates for distal sites surpass those for the cardia.[28] It has been reported that smoking is a stronger risk factor for cancer of the cardia than more distal sites,[29,30] although a site-specific effect was not observed in a recent survey in Los Angeles.[23]

Our study also found risks to be increased among pipe smokers and users of smokeless tobacco. The relation of pipe and cigar smoking to stomach cancer risk has rarely been examined, but a Louisiana study found a relative risk of 3.6 for pipe or cigar smoking among white men.[31] Information on the effects of smokeless tobacco on stomach cancer risk is also limited. The Third National Cancer Survey reported a nonsignificant relative risk of 1.7 in the highest category of smokeless tobacco use,[32] and a case-control study in Norway found increased risks associated with proximal stomach cancer only.[33] However, a case-

control study in a coal mining region of Pennsylvania found no effect for smokeless tobacco use.[34] The daily intake of tobacco-related nitrosamines by smokeless tobacco users is many times higher than amounts received by cigarette smokers.[35] Because many nitrosamines found in tobacco are animal carcinogens and are suspected to be involved in human gastric carcinogenesis,[36] further research on the relation between smokeless tobacco and stomach cancer risk would seem worthwhile.

We found no excess risk for alcohol intake, consistent with most studies of stomach cancer.[37] Only three of 13 cohort studies evaluating alcohol intake and stomach cancer have reported an association, and one of these noticed that risk was confined to persons who drank hard liquor on an empty stomach.[24]

Our study revealed increased risks associated with salted fish and bacon, consistent with associations reported with salted and preserved foods in other parts of the world.[25] These foods are relatively rich in nitrites and secondary amines that can combine to form N-nitroso compounds, some of which induce gastric tumors in laboratory animals.[38] They also are high in salt, and consumption of salty foods is frequently reported as a risk factor.[38–40] Subjects in high-risk demographic categories (immigrants and first-generation Americans, especially those with low education, and residents of the North Central states) not only tended to consume more salted fish but also had higher risks associated with salted fish intake.

Our finding of a greater than two-fold excess risk associated with high milk consumption differs from studies showing a protective effect for milk consumption in Japan[41] and among Japanese immigrants to Hawaii.[42] Milk consumption among Japanese may be highly correlated with adoption of a Western diet. Also, in our study, excess risk was associated with drinking four or more glasses a day, whereas in the Japanese studies, the upper range of milk intake was two glasses or more per day.[30,42] We excluded all stomach cancer deaths occurring before 1973 from our analysis to test the hypothesis that persons with precancerous gastric lesions may consume large quantities of milk to ease discomfort, but the risk for the upper consumption range remained elevated (RR = 2.6, CI = 1.05 to 6.3).

The excess risks we found for cooked cereal and carbohydrate intake are consistent with some case–control studies suggesting that intake of complex carbohydrates may be a risk factor for stomach cancer.[40,43] However, other studies have found no risk associated with starchy foods,[21,24] and to our knowledge, no prospective study has implicated carbohydrate consumption as a risk factor. We found the excess risk for carbohydrates to be associated primarily with deaths occurring within 6 years of questionnaire administration. This suggests that increased consumption of carbohydrates may result from gastric symptoms associated with precursor lesions or early stage cancer.

The significant association with apple consumption was unexpected. Although this may be a chance finding resulting from multiple comparisons, there was a clear dose–response effect that persisted even after controlling for education and immigrant status, and after excluding stomach cancer deaths within 5 years of the interview. Like salted fish, apples were primarily a risk factor for foreign-born and first-generation Americans and for residents of the North Central states. In this area, large quantities of apples are often stored during autumn and winter in cool outdoor pantries or underground cellars where they can become moldy. Patulin, a mycotoxin found as a contaminant of apple products, has induced sarcomas in rats at the site of subcutaneous injections, but the implication of these findings for humans has not been evaluated.[44]

Our analysis detected no significant protective dietary factors, although a number of studies have found inverse associations with consumption of fresh fruits and vegetables, vitamin C and beta-carotene, and allium vegetables.[25,36,40] Our questionnaire, developed in 1966, did not contain enough food items to capture all the food sources for vitamin C, carotenes, or most other nutrients.[17]

Several other limitations of this study must be considered. First, 23% of this cohort (4027 subjects) were lost to follow-up due to lapsed or matured policies. We compared the tobacco, alcohol, and dietary intakes of this group with those of subjects not lost to follow-up, and found no significant differences. Efforts at 11.5 years of follow-up to trace lost subjects indicated no significant difference in overall cancer mortality.[10] Second, no data were available on smoking history or diet after 1966. If smokers in this cohort followed the trend among American men in the late 1960s to early 1980s, then a substantial proportion may have quit smoking during the 20 years of follow-up, although they would still be classified as smokers in this analysis. Such a trend would tend to underestimate the effect of smoking. Third, we do not have histologic confirmation of stomach cancers, nor data on anatomical location or histologic type.

In summary, this cohort study of white men, predominantly of Norwegian, Swedish, and German ancestry, revealed elevated risks among foreign-born and first-generation Americans and residents of the North Central states. The findings are consistent with patterns from US cancer maps that have shown excess mortality in the North Central region[6] where high-risk ethnic groups are concentrated.[7] An inverse association with socioeconomic status was confined to immigrants and first-generation Americans. Furthermore, salted fish appeared to be a risk factor primarily among residents of the North Central states and among immigrants and first-generation Amer-

icans. Despite inconsistent findings in the literature, we observed a significant dose–response relationship with cigarette smoking, as well as elevated risks among pipe smokers and users of smokeless tobacco.

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